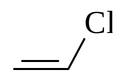
Vinyl Chloride

75-01-4



I. Physical and Chemical Properties

Description	Colorless gas or liquid
Molecular formula	CH_2=CHCl
Molecular weight	62.5
Air concentration conversion	1 ppm = 2.56 mg/m^3

II. Overview

Vinyl chloride is a known human carcinogen (reviewed by Kielhorn et al., 2000) that has been shown experimentally to be more carcinogenic in young animals than in older animals (Maltoni et al., 1981; Drew et al., 1983; Maltoni and Cotti, 1988; Cogliano et al., 1996). It is also a transplacental carcinogen in laboratory animals (Maltoni et al., 1984). It is therefore reasonable to expect that there may be a differential impact on infants and children who are exposed to this chemical.

Rodent experiments by Maltoni et al. (1981) and Drew et al. (1983) showed that animals exposed to vinyl chloride by inhalation before weaning developed more tumors and different types of tumors and with a shorter latency than animals exposed later in life. This suggests that infants and children may be more sensitive to the carcinogenic effects of vinyl chloride than are adults. For this reason vinyl chloride was considered to be a priority chemical for evaluation of potential differential effects on infants and children.

III. Principal Sources of Exposure

In 1993, the production of vinyl chloride in the United States was nearly 14 billion pounds (U.S. EPA, 1999). Vinyl chloride is used in the manufacture of numerous polyvinyl chloride products used in construction such as electrical wire and cable insulation, piping, industrial and household equipment, and medical supplies. There is heavy demand from the automobile, rubber, paper and glass industries.

Vinyl chloride has not been detected in the ambient air of California at or above a detection limit of 0.5 ppb, except for measurements taken adjacent to vinyl chloride-related industries and landfills (California Air Resources Board, 1990). For example, ambient measurements of vinyl chloride were found to range from 2 ppb to 15 ppb at 24 out of 251 landfills tested (California Air Resources Board, 1990). Ambient air exposure to vinyl chloride is expected to occur from the discharge of exhaust gasses from factories that use or manufacture the chemical, or from evaporation from areas at which chemical wastes are stored (U.S. EPA, 1999). Under calm conditions, with a vapor density of 2.15, concentrated vinyl chloride vapor may disperse slowly and flow along the ground, accumulating in low spots (Agency for Toxic Substances and Disease Registry, 1992).

IV. Potential for Differential Effects

A. Summary of Key Animal Studies

a) Mutagenicity

Vinyl chloride is mutagenic in most major short-term tests. Its activity is enhanced in the presence of exogenous or endogenous metabolic activation, suggesting that a metabolite may be more mutagenic than the vinyl chloride molecule itself (California Department of Health Services, 1990).

Following exposure via inhalation to 600 ppm vinyl chloride (4 hours per day for 5 days) 10-day-old rat pups yielded almost four times the amount of DNA adducts 7-(2'oxoethyl) guanine (OEG) and 3-ethenoguanine (EG) as did lactating adult rats (see Table 1, below) (Swenberg et al., 1992). The authors suggested that the increased relative levels of 3-ethenoguanine DNA adduct, which is a highly efficient mutagen causing G→A transitions, leads to a greater susceptibility of newborn rats compared with adult rats to vinyl chloride induced carcinogenesis.

Table 1: 7-(2'oxoethyl) guanine (OEG) and 3-ethenoguanine (EG) concentrations in rat tissue DNA measured immediately after exposure to 600 ppm vinyl chloride (based on Swenberg et al., 1992).

Tissue	OEG (pmol/μmol guanine)	EG (pmol/μmol guanine)
Pups (10 day old)		
Liver	162 ± 36	1.81 ± 0.25
Lung	20 ± 7	0.21 ± 0.08
Kidney	29 ± 1	0.31 ± 0.02
Adults (lactating females)		
Liver	43 ± 7	0.47 ± 0.14
Lung	20 ± 5	0.27 ± 0.03
Kidney	Not analyzed	< 0.12

b) Carcinogenicity

Maltoni et al. (1981) reported the results of one of the most extensive bioassays ever performed by a single institution on a single compound. This study involved nearly 7,000 animals. The design of the study was to test the effects of a wide range of variables on the carcinogenicity of vinyl chloride in rodents. The variables investigated included species (rats, mice and hamsters), strains, age and sex, routes of exposure (inhalation, ingestion, injection), doses (1 ppm to 30,000 ppm by inhalation), and schedules of treatment (early in life exposure versus later in life exposure).

Several of the experiments within the Maltoni study provide data that can address the question of the effect of age at exposure. Cogliano et al. (1996) evaluated the Maltoni data to characterize quantitatively the effects of age at exposure. For example the results for Sprague-Dawley rats exposed by inhalation to concentrations of vinyl chloride in air ranging from 0 to 12,000 ppm showed that rats exposed for five weeks beginning at 1 day old had almost a 50% incidence of angiosarcoma, whereas rats exposed for five weeks beginning at 13 weeks of age exhibited an incidence of less than 10% (see Figure 2 in Cogliano et al., 1996). Even rats exposed for 25 weeks beginning at 13 weeks of age showed an incidence of angiosarcoma of less than 10%. Sprague-Dawley rats exposed for 52 weeks beginning at 13 weeks of age had a lower incidence of angiosarcoma than rats exposed for 5 weeks beginning at 1 day of age (see Table 2 below and Figure 3 in Cogliano et al., 1996). Exposures to newborns produced hepatomas, a tumor not seen in rats exposed for 52 weeks starting at 13 weeks of age (Maltoni et al., 1981). In later experiments, Maltoni et al. (1984, 1988) demonstrated that rat fetuses and neonates had enhanced susceptibility to angiosarcomas, hepatocellular carcinomas and neuroblastomas.

Table 2: Incidence of Angiosarcomas in Rats Exposed to Vinyl Chloride by Inhalation (from Maltoni et al., 1996)

Group and concentration	Liver Angiosarcomas per 100 animals
Adults (start at 13 weeks of age)	
No treatment (control)	0 (0/60)
50 ppm	1.7 (1/60)
250 ppm	5.1 (3/59)
500 ppm	10.0 (6/60)
2500 ppm	21.7 (13/60)
6,000 ppm	22.0 (13/59)
10,000 ppm	11.7 (7/60)
Newborns	
6,000 ppm	40.5 (17/42)
10,000 ppm	34.1 (15/44)

note: Adults were exposed for weeks 14 to 65; newborns were exposed for weeks 1 to 5.
See also Cogliano et al., 1996, Figure 3.

Cogliano et al. (1996) reviewed earlier experimental studies by Drew et al. (1983) and Maltoni et al. (1981). They conclude, "A study of partial-lifetime exposures in these animal species suggests that the lifetime risk of cancer depends on the age at exposure, with higher lifetime risks attributable to exposures at younger ages. Studies of newborn animal exposures further demonstrate that a brief exposure in newborns can, by the end of life, induce a higher incidence of tumors compared to long-term exposure occurring later in life, including tumor types not induced by exposure later in life."

Drew et al. (1983) looked at the effect of age and exposure duration on vinyl chloride oncogenicity in females of several different species of rodents. Groups of female CD-1 Swiss mice, B6C3F1 mice, Fischer 344 rats, and Golden Syrian hamsters (N = 54 for mice, N = 56 for rats and hamsters) were exposed to vinyl chloride for six hours/day, five days/week for six, 12, 18, or 24 months, beginning at eight weeks of age, and observed for their lifespans. Other groups were held until six or 12 months of age, exposed for six or 12 months, and then observed for the remainder of their lifespans. The exposures were conducted at a single dose level for each species; mice, rats and hamsters were administered 50, 100, and 200 ppm, respectively. All animals exposed to vinyl chloride at age eight weeks (the start of the experiment) exhibited decreased survival relative to controls (Drew et al., 1983). B6C3F1 mice experienced the most significant shortening of lifespan regardless of the age at which exposure was begun. No significant decrease in survival was observed in rats, hamsters, or Swiss mice initially exposed after six months of age. Other clinical signs of vinyl chloride toxicity were not evident and liver necrosis was not observed.

In rats, exposure to vinyl chloride (100 ppm) was associated with hemangiosarcomas, mammary gland adenocarcinomas and adenomas, and hepatocellular carcinomas (Drew et al., 1983). The incidence of hemangiosarcomas was a function of the duration of exposure; the longer the exposure period the greater the incidence of hemangiosarcomas. A six-month exposure produced a low incidence of hemangiosarcomas and hepatocellular carcinomas only if begun early in life. No hemangiosarcomas and only one hepatocellular carcinoma were produced when six-month exposure was started in 12 or 18-month-old animals. One-year exposures produced a significant incidence of tumors, especially if begun early in life. The incidence of mammary gland adenocarcinomas and fibroadenomas was not always related to exposure duration, but the incidence was higher in rats whose exposure began at eight weeks of age. Hepatocellular carcinomas were induced in a dose-related manner in rats when exposures began at eight weeks.

In hamsters, hemangiosarcomas, mammary gland carcinomas, stomach adenomas, and skin carcinomas were associated with exposure to 200 ppm vinyl chloride (Drew et al., 1983). The highest incidence of hemangiosarcomas and stomach adenomas occurred in animals exposed early in life for only six months. The highest incidence of mammary gland carcinomas was seen in animals exposed at an early age for up to twelve months. Exposure beginning at or after eight months of age resulted in a markedly lower tumor incidence, probably because the lifespans of chronically exposed hamsters were significantly reduced to the point that late-appearing tumors would not be expressed.

Mice appeared to be the species most sensitive to the carcinogenic effects of vinyl chloride (50 ppm) (Drew et al., 1983). Hemangiosarcomas and mammary gland carcinomas in B6C3F1 and Swiss mice, and lung carcinomas in Swiss mice only were associated with vinyl chloride exposure. In B6C3F1 mice, exposure to vinyl chloride for six months resulted in 60-70 percent incidence of hemangiosarcomas, regardless of the age at exposure initiation. The incidence of mammary gland carcinomas in B6C3F1 mice was greatest when the animals were exposed early in life. Lower incidences of this tumor were seen when initial exposure occurred at a later age. In Swiss mice, exposure to vinyl chloride at an early age resulted in the highest incidence of hemangiosarcomas, mammary gland carcinomas, and lung carcinomas, regardless of duration of exposure. Lower incidences of all tumors were observed in animals exposed later in life.

In vinyl chloride-induced rat liver angiosarcomas, Ki-ras mutations were not observed (as they were in vinyl chloride induced angiosarcomas in humans) but 44 percent did have p53 mutations (Froment et al., 1994). The mutations in liver tumors caused by vinyl chloride are distinct from those detected in sporadic liver cancers. The data available at present suggest that etheno adducts may initiate the oncogenic process following exposure to vinyl chloride. Animal studies indicate that young animals are more sensitive than adults to the formation of these adducts (Swenberg et al., 1992).

The animal experiments of Drew et al. (1983) and Maltoni et al. (1981) clearly indicate that exposure to vinyl chloride early in life has a more potent effect than exposure later in life or exposure distributed throughout the lifetime of the animal. Applying these results to humans would suggest that exposure to infants and children might have a significantly greater carcinogenic effect than exposure to older people. At present this increased potential susceptibility of children to the carcinogenic effects of vinyl chloride has not been incorporated directly into the formula for calculating cancer risk for vinyl chloride. In determining a cancer risk value for vinyl chloride, California Department of Health Services (CDHS, 1990) acknowledged that newborn animals showed greater sensitivity to the carcinogenic effects of vinyl chloride than older animals. CDHS used this as a rationale for choosing a value for cancer unit risk (2×10^{-4} ppb^{-1} or 7.8×10^{-5} $m^3/\mu g$) that was at the top of a range of values calculated from human and animals studies (2.5×10^{-5} to 2×10^{-4} ppb^{-1}).

c) Reproductive and Developmental Toxicity

John et al. (1977) tested for effects of maternally inhaled vinyl chloride on embryonic and fetal development in rodents. Pregnant CF-1 mice, Sprague-Dawley rats and New Zealand white rabbits were exposed to 500 ppm of vinyl chloride for seven hours per day during the period of major gestational organogenesis. Other groups of mice and rabbits were exposed to vinyl chloride concentrations of 50 and 2500 ppm. Fetotoxicity occurred in mice at 500 ppm, and the effects included increased fetal resorption, decreased fetal body weight, reduced litter size, and retarded cranial and sternebral ossification. Rat offspring showed decreased body weight at 500 ppm maternal exposure and dilated ureters at maternal exposure to 2500 ppm. No sign of maternal or developmental toxicity was observed in rabbits at either concentration (John *et al.*, 1977).

B. Summary of Key Human Studies

a) Reproductive and Developmental Toxicity

Several epidemiological studies have been conducted to assess potential reproductive and developmental effects in the families of vinyl chloride workers (California Department of Health

Services, 1990). Edmonds et al. (1975, 1978) conducted two case-control studies evaluating central nervous system malformations among offspring of vinyl chloride workers and families living near polyvinyl chloride facilities in Indiana and West Virginia. More cases than controls lived within three miles of the polyvinyl chloride plants ($p<0.02$). Mothers living in Ohio communities with PVC production facilities gave birth to an excess number of children with congenital malformations as compared to the expected number based on the state average or based on the experience in the balance of the counties in which these cities are located (Infante, 1976). In a review of epidemiological studies related to vinyl chloride exposure, Hemminki and Vineis (1985) concluded that there was inadequate evidence linking environmental or paternal exposures to vinyl chloride with birth defects.

b) Carcinogenicity

Creech and Johnson (1974) described three cases of liver angiosarcoma in workers at a Kentucky rubber plant. Because liver angiosarcoma is a rare tumor (20 to 25 cases per year in the U.S.), the clustering of three cases in one facility indicated an abnormally high incidence of this cancer. Based on this report, and animal studies, multiple studies of workers exposed to vinyl chloride were conducted. By 1999 there had been over twenty epidemiological studies relating vinyl chloride to various cancers.

The association between vinyl chloride exposure and increased risk for other cancers is not as clear as that for liver cancer. Some evidence associates exposure to vinyl chloride with increased mortality ratios for brain cancer, lung cancer, and lymphoma. Since these cancers appear more commonly in the general population than liver angiosarcoma, it becomes more difficult to demonstrate increased risk due to exposure (California Department of Health Services, 1990).

There is some indication that workers exposed to vinyl chloride may be at greater risk for brain cancer. The studies that relate to this question are summarized in Table 14 of the Public Health Goal document (OEHHA, 2000a). Five studies found a statistically significant positive association between brain cancer and vinyl chloride exposure ($p<0.05$) (Byren et al., 1976; Waxweiler et al., 1976; Equitable Environmental Health, 1978; Weber et al., 1981; Cooper, 1981). Brain cancer incidence increased an average of four-fold above that expected for the general population in these five studies. Other studies found no association (OEHHA, 2000a, Table 14). Some later papers included in Table 14 re-examined the data from the earlier studies. The question of the association, if any, between vinyl chloride exposure and brain tumors as well as other non-liver cancers should be the subject of a future meta-analysis.

The evidence linking vinyl chloride exposure to lung cancer remains inconclusive. Analyses of SMRs for cancer of the lung were performed in 12 studies. Of these, seven studies showed an increased risk for lung cancer, but only one was statistically significant at the 5 percent level (Buffler et al., 1979). This increased risk persisted after adjusting for personal smoking habits (for this particular cohort). However, this cohort was small and the study was unable to demonstrate an increased risk for any other cancer.

An association between vinyl chloride exposure and lymphoma has not been established. Five studies evaluated the risk of lymphoma development among workers occupationally exposed to vinyl chloride.

Four of the studies showed a positive trend for lymphoma among vinyl chloride workers, but only Weber et al. (1981) noted statistical significance. However, the statistical power in all of these studies was less than 80 percent to demonstrate a relative risk of two, and less than 40 percent to show a relative risk of 1.5 (California Department of Health Services, 1990).

In human cases of angiosarcoma of the liver induced by vinyl chloride, mutations have been found in the p53 and Ki-ras genes (reviewed by Kielhorn et al., 2000). Similar studies have been conducted in animals (see below under "mutagenicity" and "carcinogenicity").

There is ample evidence that vinyl chloride is carcinogenic in humans. However, there is no direct human evidence indicating that infants or children would be more sensitive than adults. There is evidence for a differential effect on young animals from the Maltoni and Drew studies (above).

V. Regulatory Background

An acute Reference Exposure Level (REL) for vinyl chloride of 180,000 µg/m^3 has been adopted by OEHHA (OEHHA, 1999). This REL is based on subjective reports of mild headaches and dryness of eyes and nose in human volunteers (Baretta et al., 1969). OEHHA has developed a Public Health Goal (PHG) of 0.05 mg/L (or ppb) for vinyl chloride in drinking water (OEHHA, 2000a). The PHG is based on carcinogenic effects observed in an inhalation study by Drew et al. (1983), wherein the authors observed an increase in lung carcinoma incidence in female Swiss mice exposed to vinyl chloride. The PHG was calculated from a cancer slope factor of 0.27 (mg/kg-day)$^{-1}$ developed under the Toxic Air Contaminant Program by the California Department of Health Services (1990).

Vinyl chloride is listed under the California Safe Drinking Water and Toxics Enforcement Act of 1986 (Proposition 65) as a chemical known to the State to cause cancer (OEHHA, 2000b). It is not listed as a developmental or reproductive toxicant.

VI. Conclusions

Vinyl chloride may be more carcinogenic to infants and children than to adults, based on the results of animal studies by Drew et al. (1983) and Maltoni et al. (1981). These studies showed that animals that were exposed to vinyl chloride pre-weaning developed more tumors with a shorter latency than animals that were exposed later in life, and that they developed types of tumors not seen in the later-exposed animals. This was not due simply to longer time for tumor development in the younger mice as evidenced by the analysis of Cogliano et al. (1996) and Maltoni's own analyses (Maltoni et al., 1981, 1984 and 1988).

While measurements of vinyl chloride in ambient air suggest levels below the limit of detection, there may be localized exposures due to emissions from PVC manufacturing or landfills. Thus, while not a general ambient air concern, vinyl chloride emissions from local hotspots may be higher. Should information become available indicating that local exposures are significant, OEHHA may revisit listing vinyl chloride under SB 25.

VII. References

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